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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,483	10/07/2004	Hiroyuki Miyata	0283-0200PUS1	7464

2292 7590 01/22/2008
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EXAMINER

HANLEY, SUSAN MARIE

ART UNIT	PAPER NUMBER
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1651

NOTIFICATION DATE	DELIVERY MODE
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01/22/2008

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary

Application No.

10/510,483

Applicant(s)

MIYATA ET AL.

Examiner

Susan Hanley

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

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DETAILED ACTION

The amendment and remarks filed 8/20/07 are acknowledged.

Election/Restrictions

It is again ~~stated~~ ^{STATED} that the specie elections were withdrawn in the last Office action.

Claims 1-19 are under examination.

Specification

The amendment filed 8/20/07 overcome the objection to the specification regarding trademarks.

Priority

The amendment to the specification for the benefit of a prior-filed application under 35 U.S.C. 120, 121 or 365(c), is acknowledged.

Response to Arguments

Applicant's arguments filed 8/20/07 have been fully considered but they are moot based on new grounds of rejection. Applicant's arguments will be addressed insofar as they apply to the new grounds of rejection.

Claim Rejections - 35 USC § 112

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claim 1 has been amended to recite "a hydrolase capable of catalyzing the hydrolysis of said enantiomer". New claims 13-19 further describe the type of hydrolase and microorganism source.

Applicant argues that the addition of the phrase "capable of catalyzing the hydrolysis of said enantiomer" to claim 1 overcomes the rejection.

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Applicant's assertion that the amendment to claim 1 over come the rejection has been considered and is deemed unpersuasive. With the exception of lipase from *Candida antartica* (Chirazyme L-2TM) and a *Pseudomonas* lipase from Amano PS, the specification fails to describe other hydrolases that may have required stereoselective hydrolytic activity. The recitation of a "hydrolase capable of carrying out the hydrolysis" still fails to provide an adequate written description of the desired because the as-filed specification provides no specific description for the vast majority of the claim-encompassed hydrolases that are capable of catalyzing the claimed resolution. The specification discloses that lipases, esterases and proteases can be isolated from yeast or bacteria may catalyze the claimed reaction. The use of the term "originating" in claims 3, 9 and 14-19 implies that the preparation of a multitude of genetically recombined organisms that produce a lipase with the desired activity is disclosed by the as-filed specification. Therefore, the claims encompass the use of numerous potential hydrolases to carry out the claimed reaction. However, there is no specific written description for the use or preparation of hydrolases other than lipase from *Candida antartica* (ChirazymeTM) which Applicant actually demonstrates as having the required stereoselective hydrolytic activity. Applicant suggests that and a *Pseudomonas* lipase (Amano PSTM) may have the desired activity. Moreover, the sole example using the lipase from *Candida antartica* (Chirazyme L-2TM) and suggesting that a *Pseudomonas* lipase from Amano PS can serve as biocatalysts does not provide a representative sample of the hydrolases encompassed by the claims, given the huge variation in catalytic properties of hydrolases that are encompassed by the current broad claim language. Because the claims encompass a multitude of hydrolases neither contemplated nor disclosed by the as-filed disclosure, it is clear that applicant was not in possession of the full scope of the claimed subject matter at the time of filing.

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Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for resolving a racemic mixture containing an N-aryl substituted beta-amino acid or an N-aryl substituted-2-homopipicolinic acid by selectively hydrolyzing one enantiomer with a hydrolase which is a lipase from *C. antarctica* (Chirazyme L-2TM) obtained from Roche, does not reasonably provide enablement for the a process for resolving a racemic mixture containing an N-aryl substituted beta-amino acid or an N-aryl substituted-2-homopipicolinic acid by selectively hydrolyzing one enantiomer with any hydrolase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a process for resolving a racemic mixture containing an N-aryl substituted beta-amino acid or an N-aryl substituted-2-homopipicolinic acid by selectively hydrolyzing one enantiomer with a hydrolase. The specification shows that the lipase Chirazyme L-2TM from *C. antarctica* can successfully catalyze the stereoselective ester hydrolysis of beta-amino acids or 2-homopipicolinic acids having N-aryl substitution. The disclosure does not provide a further definition of Chirazyme L-2TM. However, the Dicosimo et al. (US 5,928,933; disclosed in the IDS filed 10/7/04) identifies it as lipase fraction B from *C. antarctica* (see Table 7, for example). The specification discloses that lipase originated from *Pseudomonas Amano PS* is preferred for catalyzing the reaction but does not provide an example of this capability.

The specification discloses neither other hydrolases that are capable of carrying out the claimed reaction nor a method that does not require undue experimentation to select other stereoselective hydrolases. The prior art demonstrates that the selection of hydrolases that can carry out ester hydrolysis is unpredictable. For example, Dicosimo et al. discloses the resolution of

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diastereomeric mixtures of N-(alkoxycarbonyl)-4-keto-D,L-proline alkyl esters with a number of lipases, proteases and esterase. However, it is clear from the results in Tables 2-7 that Chirazyme L-2TM can carry out the reaction with a number of substrates but that many of the other lipases, proteases or esterases were unable to catalyze the stereoselective hydrolysis while other hydrolases had low racemate conversion or yielded a product with a low % de. Example 13 (Table 7) demonstrates that Chirazyme L-2TM is the only lipase from *C. antarctica* that provides any product at all. It is also notable that In view of the lack of any specific guidance with respect to identifying other hydrolases that can catalyze the claimed reaction, the skilled artisan would expect to have to undertake a trial and error process such as screening to determine which of the multitude of hydrolases by the claims would be amenable to the techniques disclosed in the instant application. Such a trial and error process clearly amounts to undue experimentation.

The limited showing of one type of lipase having a particular stereoselective enzymatic activity is not sufficient to enable a claim drawn to the stereoselective hydrolysis by any possible hydrolase because the art of Enzymology is too unpredictable. The determination of how enzymes with interact with substrates requires an understanding of the catalytic mechanism and the characterization of the active site and the topology of the enzyme in order to understand how various molecules bind to the enzyme and/or be chemically changed by the enzyme in question. At the time of the invention, stereoselective ester hydrolysis in general was known. However, as shown by the Dicosimo patent, the interaction of hydrolases with substrates to effect stereoselective resolution is not predictable.

There is no method that predicts what hydrolases will catalyze the desired stereoselective hydrolysis of the claimed N-aryl substituted substrates as described in the specification. It is well

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known in the art that enzymatic activity and specificity is complex. There is no predictable way for a skilled artisan to know in advance what hydrolases will have the desired stereoselective activity as set forth in the instant application. The limited disclosure cannot be extrapolated by the skilled artisan to predict when the disclosure is enabling for identifying said stereoselective hydrolases. It would require one of ordinary skill in the art undue experimentation to predict what hydrolases will catalyze the desired stereoselective hydrolysis of the claimed N-aryl substituted substrates according to the directions of the instant disclosure. Thus, claims 1-19 are not commensurate in scope with the enabling disclosure.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9 recite the limitation that " R^1 and R^2 may be bonded to form a ring" in line 12 of the claim. This limitation allows for a ring of any size to be formed by the bonding of R^1 and R^2 . With the exception of a 6-membered ring, there is insufficient antecedent basis for this limitation in the claim because the preamble and lines 4 and 5 in the body of claim 1 are drawn to a N-substituted β -amino acid alkyl ester (no ring) or a N-substituted 2-homopiperic acid ester (also known as 2-piperidine carboxylic acid) which is based on piperidine, a 6-membered ring. There is no antecedent basis for rings of other sizes.

Claim 1 is rejected because it is unclear how R^1 and R^2 can be bonded when R^2 is hydrogen. Hydrogen makes only one bond.

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Claims 1 and 6-10 are rejected because the phrase "represented by the formula" is vague and indefinite. The term "represented" is not defined by the specification or the MPEP as an open or closed transitional term. Thus, absent an explicit definition, the metes and bounds of any sentence that employs said phrase is undefined.

Claims 6-10 are rejected because they employ the phrase "wherein Ar, R¹, R², R³, R⁴ and R⁵ have the same meanings as defined above" is vague. The use of the term "above" implies that the definitions are in the text of the instant claim whereas the meanings of these variables are defined in claim 1.

Claims 2-5 and 11-19 are dependent claims that do not overcome the deficiencies of the independent claim that they are dependent therefrom.

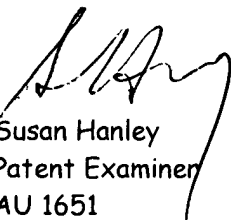
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Susan Hanley
Patent Examiner
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